

### *Remarks*

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 52-59, 61-68 and 71-78 are pending in the application, with claims 52 and 75 being the independent claims. Claims 69 and 70 have been canceled.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider and withdraw the outstanding rejections.

#### *I. Claim Rejections Under 35 U.S.C. § 102(b)*

Claims 52-58, 62, and 66-68 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Boyd (*Nucleic Acid Research*, 21:817-821 (1993).) (Office Action, page 3.) Applicants respectfully disagree.

Claims 52-58, 62 and 66-68 are directed to methods that involve contacting a linear nucleic acid with an adapter having a first site-specific recombination site to make an "adapterized" nucleic acid having one or more adapters at one or more termini (*see*, steps (a) and (b) of claim 52), and recombining the "adapterized" nucleic acids with a vector having a second site-specific recombination site (*see*, step (c) of claim 52). Step (c) of the recited methods results in the intermolecular recombination between the first and second site specific recombination sites. On page 5 of the office action, the Examiner asserts that Boyd teaches step (c) on page 819, first column, first full paragraph and in Figure 2. The method of Boyd is a two stage process where in the first stage a DNA fragment is ligated, at both ends, to a plasmid vector containing a *lox* site resulting in the formation of a linear DNA

molecule. In the second stage, *Cre* recombinase is added resulting in the formation of a circular DNA molecule consisting of the *lox* containing plasmid vector and the DNA fragment. It should be noted that Boyd does not teach "mixing said linear nucleic acid molecule with at least one vector comprising at least a second site specific recombination site" as recited by step (c) of claim 52. Boyd describes the circularization of a single linear DNA molecule using an intramolecular recombination reaction. Because step (c) of claim 52 recites mixing a linear nucleic acid molecule with a vector comprising a second site specific recombination site, it is clear that recombination is occurring between recombination sites on two separate molecules and is therefore an intermolecular recombination reaction. Thus, Boyd does not anticipate claims 52-58, 62 and 66-68. Applicants respectfully request that the Examiner reconsider and withdraw the rejection of these claims under 35 U.S.C. §102 over Boyd.

## II. Claim Rejection Under 35 U.S.C. § 103(a)

Claims 61-65, 71-72, 74-76, and 78 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Boyd, in view of Alonso *et al.* (*FEMS Microbiology Letters*, 142:1-10 (1996).) (Office Action, page 7.) Claims 59, 61-62, 71-73, and 75-77 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Boyd, in view of Waterhouse *et al.* (*Nucleic Acids Research*, 21:2265-2266 (1993).) (Office Action, page 7.) Applicants respectfully disagree.

Establishment of *prima facie* obviousness requires a showing that each claim element is taught or suggested by the prior art. (*See In re Royka*, 180 USPQ 580 (CCPA 1974).) Absent a showing of such motivation and suggestion, *prima facie* obviousness is not

established. (*See In re Fine*, 5 USPQ2d at 1598.) A prior art reference must be considered in its entirety, *i.e.* as a whole, including portions that teach away from the claimed invention. (*W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)). The Court of Appeals for the Federal Circuit further instructed that "references that teach away cannot serve to create a *prima facie* case of obviousness" (*In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)), and that an "applicant may rebut a *prima facie* case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect." (*In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997).)

Claims 59 and 61-65 (which depend from claim 52) recite methods that involve the intermolecular recombination between an "adapterized" linear nucleic acid and a vector. Similarly, claims 71-78 recite methods for making nucleic acid molecules having two or more site-specific recombination sites that do not recombine with each other.

The teachings of Boyd are incompatible with the presently claimed inventions. Boyd teaches a two stage process where a DNA fragment is ligated at both ends to a plasmid vector comprising a *lox* recombination site and then *Cre* recombinase is used to catalyze an intramolecular recombination reaction to create a circular DNA molecule. The construction of these circular molecules specifically requires intramolecular recombination. The intramolecular recombination methods disclosed in Boyd cannot be used for the intermolecular recombination methods recited by claims 59 and 61-65. Because the molecules described in Boyd are constructed using intramolecular recombination they are required to have recombination sites which are capable of recombining with each other. This is the opposite of the molecules recited by claims 71-78, which have recombination

sites that do not recombine with each other and are specifically designed for intermolecular recombination. The intramolecular recombination reactions disclosed by Boyd cannot be performed using the nucleic acid products of the methods recited by claims 71-78.

In view of the above remarks, it is clear that Boyd teaches away from the presently claimed invention. Accordingly, as instructed by The Court of Appeals for the Federal Circuit, Boyd cannot serve as the basis for a proper §103 rejection. Neither Alonso *et al.* nor Waterhouse *et al.* provide disclosures that would allow the intramolecular recombination reactions disclosed by Boyd to be used with the present claims. Therefore Alonso *et al.* and Waterhouse *et al.* may not be used to cure the defects of Boyd.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a).

*Conclusion*

All of the stated grounds of rejection have been properly traversed. Applicants therefore respectfully request that the Examiner reconsider and withdraw all presently outstanding rejections. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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